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Morphology Rounds at the University of Rochester

Unusual Anemias

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CASE 1: COPPER DEFICIENCY

Case Description

The patient is a 52-year-old white female who was seen in consultation for anemia. Past medical history was remarkable for multiple abdominal surgeries including hysterectomy, partial gastrectomy for peptic ulcer disease, cholecystectomy, and two bowel resections to relieve obstruction and perforation. Since her last bowel resection one year prior, she had developed dumping syndrome, malnutrition, and weight loss of more than 20 pounds. She was placed on antibiotics as well as Donnatal, Pancrease, ferrous sulfate, folic acid, and monthly Vitamin B_{12} injections, and on her own, she took multivitamins, zinc, and calcium supplements. Over the ensuing months, she regained weight from 73 to 90 pounds at about one month prior to evaluation. On physical examination, she was somewhat malnourished, pulse rate and blood pressure were normal, hair was thin, lungs clear to percussion and auscultation, heart normal, abdomen soft and non-tender without palpable organomegaly or masses, no petechiae present, and neurologic exam unremarkable. Review of prior laboratory data revealed a hematocrit of 26% one year before and 31% one month before, but only 25% at the time of evaluation, with a mean red blood cell volume (MCV) of 105 fl. The white blood cell count was 2,500/μl, down from 7,000/μl one month previously, but the platelet count was 334,000/μl. Serum LDH was slightly elevated at 274 MU/ml (normal 100–240); serum uric acid, creatinine, total protein, and albumin were all normal. Her serum copper level was 20 μg/ml (normal 80–155) and zinc level 114 μg/ml (normal 50–160).

The peripheral blood smear showed anisocytosis and poikilocytosis with a population of microcytic, hypochromic cells, and numerous red cells containing Pappenheimer bodies (Fig. 1A). The white cell differential was normal. A bone marrow aspirate revealed vacuolated erythroid and myeloid precursors (Fig. 1B) and the iron stain showed numerous ring sideroblasts (Fig. 1C).

Comment

The peripheral blood and bone marrow morphology in this case were diagnostic of a sideroblastic anemia. In addition, the leukopenia and the presence of vacuoles in the myeloid and erythroid precursors were typical of those described in copper deficiency states [1] but are also seen in ethanol abuse, chloramphenicol exposure, stem cell disorders, and chemotherapy effect. The potential causes of both acquired sideroblastic anemia and the vacuolated changes include copper deficiency, ethanol use, and myelodysplastic syndromes. This patient had no history of ethanol use but the malnutrition secondary to bowel resection and the history of zinc ingestion represented a potential for copper deficiency as the cause of the sideroblastic anemia and neutropenia [2].

The ubiquitous distribution of copper and low daily requirements make dietary copper deficiency extremely rare. As copper absorption occurs in the small intestine, copper deficiency may occur after prolonged parenteral alimentation without copper supplementation, in adults with short bowel and malabsorption syndromes [3], and in marasmic infants. Dietary zinc and especially supplemental zinc interact with copper in a competitive manner, thereby increasing fecal copper loss [2].

This patient was instructed to discontinue zinc supplementation and begin copper sulfate at 5 mg each day orally. Her serum copper level normalized over the course

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of about 4 weeks; her white blood cell count recovered to 4,600/μL and hematocrit rose to 36%.

Although the blood zinc level was not elevated, zinc supplementation probably contributed to the copper deficiency by interference with copper absorption. The complete correction of the patient's anemia and neutropenia by copper supplementation confirms the etiology as copper deficiency.

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CASE 2: HEREDITARY SIDEROBLASTIC ANEMIA MISTAKENLY DIAGNOSED AS THALASSEMIA INTERMEDIA

Case Description

A 38-year-old Greek-American male carried the diagnosis of "thalassemia intermedia" with a baseline hematocrit of 20% and a mean red blood cell volume (MCV) of 51 fl. He had never received blood transfusions. A long-standing history of moderate to massive hepatosplenomegaly was evaluated by magnetic resonance imaging, which showed a hepatic nodule, and liver biopsy revealed nodular cirrhosis and iron deposition (iron stain strongly positive for hemosiderin) in hepatocytes. The serum ferritin level was 5,200 ng/ml and nightly subcutaneous desferrioxamine was initiated. Because of the marked hemosiderosis without a history of blood transfusion, the family was screened for hemochromatosis, and studies indicated that two sisters had β-thalassemia trait with normal ferritin levels but a brother had a ferritin of 3,000 ng/ml and a hematocrit of 22% with microcytic red cell indices.

The patient's peripheral blood smear show marked poikilocytosis with bizarre red cell shapes, marked hypochromia, and frequent red cells containing Pappenheimer bodies (Fig. 2A). Bone marrow aspirate showed a hypercellular marrow with numerous ring sideroblasts (Fig. 2B). The hematocrit increased to 24% after initiation of pyridoxine therapy (100 mg/day). The patient's brother also underwent a bone marrow exam which was consistent with sideroblastic anemia.

Comment

The congenital sideroblastic anemias have several characteristic morphologic features [1]. Hypochromia and microcytosis can be quite pronounced (MCV $<$ 60 fl), with or without severe anemia. Wright's staining of the peripheral blood reveals red cell inclusions (Pappenheimer bodies, Fig. 2A) that reflect the presence of iron and possibly precipitated ribosomes. Prussian Blue staining of the bone marrow reveals characteristic ring sideroblasts, particularly in the late erythroid precursors, resulting from deposition of iron in the mitochondria. The morphologic criteria for ring sideroblasts include having at least five siderotic granules per cell, encircling at least one-third of the nucleus.

These morphologic changes are attributable to a deficiency in heme synthesis which in cases of hereditary X-linked sideroblastic anemia can involve δ-aminolevulinate synthase, the enzyme which binds to the cofactor pyridoxal phosphate. Some of these patients can respond to pyridoxine therapy [2,3]. A frequent feature in these patients, well illustrated in our case, is the development of increased tissue iron, including extramedullary sites, which can resemble hereditary hemochromatosis [4].

It is not surprising that this patient was initially diagnosed to have thalassemia intermedia. The red cells in both thalassemia intermedia and congenital sideroblastic anemia are microcytic and hypochromic and both conditions can show target cells and basophilic stippling. However, careful examination of the peripheral blood smear revealed extreme hypochromia and typical Pappenheimer bodies. Extreme iron overload in the absence of red cell transfusions was an additional clue to the diagnosis. Definitive diagnosis of sideroblastic anemia required the demonstration of characteristic ring sideroblasts in the bone marrow aspirate.

In the case of sideroblastic anemia, it is important to distinguish between congenital and acquired forms, the latter secondary to states such as myelodysplasia, alcohol use, copper deficiency, zinc toxicity, or drug-related (antituberculous drugs, penicillamine, progesterone, chloramphenicol).

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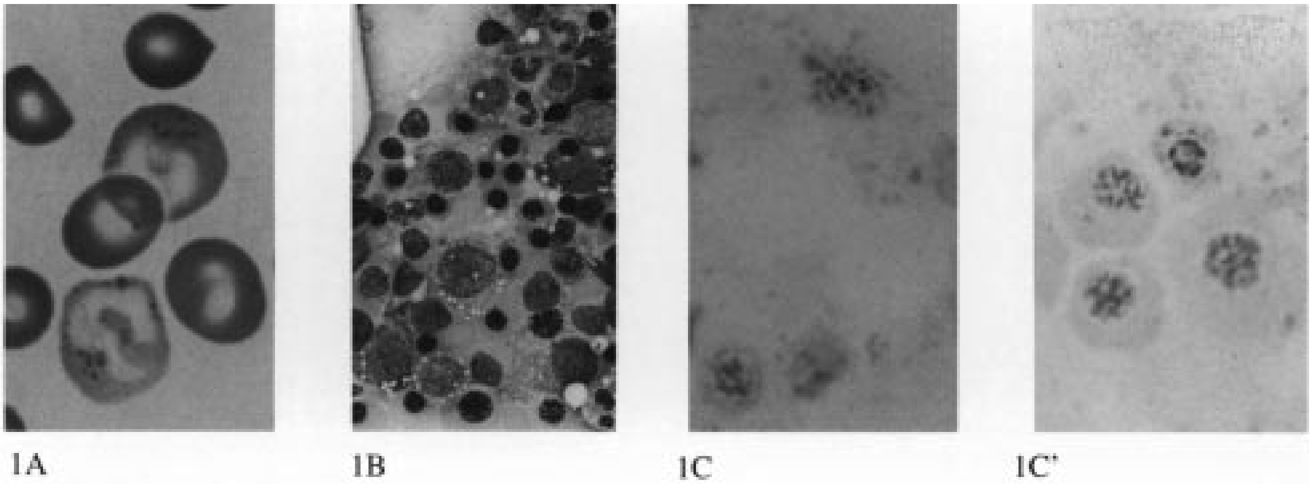
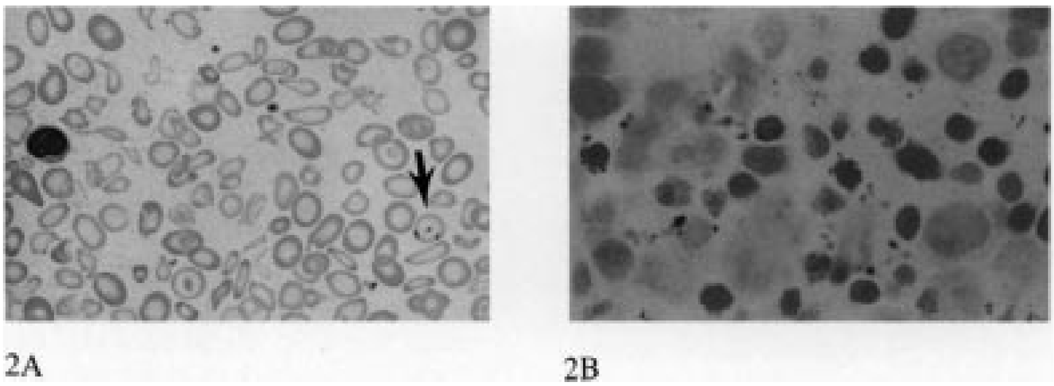
Figs. 1–3. Fig. 1. A: Peripheral blood smear (Wright-Giemsa) showing two red cells with Pappenheimer bodies. B: Bone marrow aspirate smear (Wright-Giemsa) showing vacuolated erythroid and granulocytic precursors. C, C': Prussian Blue stain of bone marrow aspirate showing ring sideroblasts. Fig. 2. A: Peripheral blood smear showing marked poikilocytosis, hypochromia and red cells containing Pappenheimer bodies (see arrow). B: Prussian Blue stain of bone marrow biopsy showing numerous ring and pathologic sideroblasts. Fig. 3. Peripheral blood smear showing anisopoikilocytosis (A) and coarse basophilic stippling (B). Bone marrow aspirate smear (Wright-Giemsa stain) showing striking megaloblastoid chromatin, nuclear budding, internuclear chromatin bridges (arrow, C), and bi- and multinucleated erythroid precursors (D).

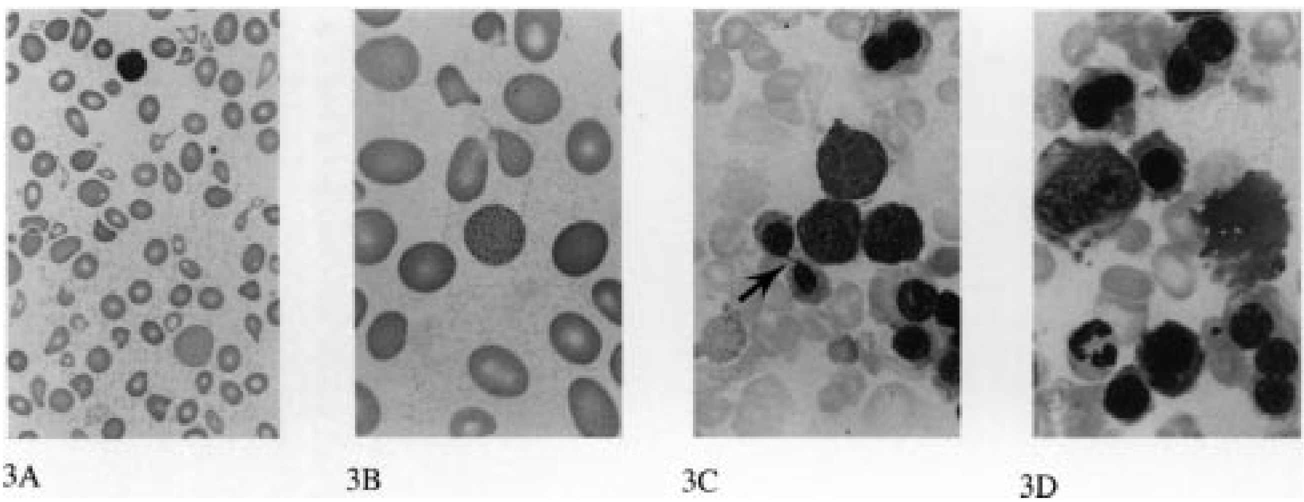
Case 1: Copper Deficiency



Case 2: Hereditary Sideroblastic Anemia



Case 3: Congenital Dyserythropoietic Anemia



Figs. 1–3.

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CASE 3: CONGENITAL DYSERYTHROPOIETIC ANEMIA

Case Description

The patient is a 32-year-old white male evaluated initially as a young child when pallor and signs of anemia were noted. Throughout his lifetime, his course has been characterized by modest anemia with hematocrit values of 25%–28%, splenomegaly, and hyperbilirubinemia resulting in pigment gallstones and cholecystectomy at an early age. He had required minimal transfusion support but developed secondary iron overload as evidenced by a serum ferritin concentration of 1100 ng/ml. He was started on desferrioxamine therapy for presumed iron overload.

His diagnostic evaluation began as a youngster and was quite extensive. He was seen by a number of hematologists and samples of his blood and bone marrow were evaluated in different centers in the United States. The peripheral blood and bone marrow morphology was reviewed (Fig. 3), and the following laboratory tests were performed and were normal: red cell enzyme determinations, G6PD determination, autohemolysis, heat unstable hemoglobin for hereditary pyro-poikilocytosis, red cell chromium survival, and acidified serum hemolysis (HAM) test. Serologic tests were notable for a positive anti-I and a negative anti-i. The beta:alpha globin synthetic ratio was abnormal (0.66, normal range 0.9–1.1).

Comment

This patient has many features suggestive of Type I congenital dyserythropoietic anemia (CDA). The additional abnormality in globin chain synthesis suggests a congenital hemolytic anemia similar to that described by Weatherall et al. [1] however abnormal globin synthesis may also be a feature of Type I CDA [2]. Congenital dyserythropoietic anemias are characterized by ineffective erythropoiesis, tissue siderosis, and a variety of morphologic features, most notably erythroid multinuclearity [3]. Three types of CDA have been described. Type I is an autosomal recessive disorder which can be differentiated from type II (HEMPAS) by morphologic features and by serologic profile. Morphologic features of Type I CDA include abnormal erythroid cells with megaloblastoid changes, internuclear chromatin bridges, and incomplete division of nuclei or binucleated cells. Multinuclearity of erythroid precursors is not seen in this type. Electron microscopic features include widened nuclear pores, cytoplasmic microtubule formation, invasion of the cytoplasm by nuclear material, and ribosomal disaggregation [4]. Type II CDA is characterized by erythroblast multinuclearity and a positive acid hemolysis test. Type III CDA is an extremely rare disorder that is frequently autosomal dominant, and is characterized by marked erythroblast multinuclearity and basophilic stippling. Clinical features vary from mild anemia to a transfusion-dependent state.

Most patients with Type I CDA are recognized during infancy or childhood and have anemia and splenomegaly. There is no effective treatment available; most patients do not require transfusion support and splenectomy is unlikely to have a beneficial effect. Erythroid multinuclearity is helpful in distinguishing CDA from thalassemic disorders; however, in type I CDA the bone marrow findings may be more subtle than in type II or type III CDA. This patient has had a fairly typical clinical course and developed secondary iron overload—a recognized complication of many congenital hemolytic disorders that are associated with ineffective erythropoiesis.

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